UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,997	06/23/2000	IMRE KOVESDI	204526	8984

23460 7590 09/10/2003

LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6780

EXAMINER
MCKELVEY, TERRY ALAN

ART UNIT	PAPER NUMBER
1636	18

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,997	KOVESDI ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/21/03, 3/11/03, and 6/20/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,8,9,11-27 and 38-44* is/are pending in the application.

4a) Of the above claim(s) *9,16,17,22,23 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,8,11,12,15,18-21,24-27,38-41,43 and 44* is/are rejected.

7)☒ Claim(s) *13 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/21/03 has been entered.

Election/Restrictions

Applicant's election with traverse of a replication-deficient adenoviral viral vector comprising a nucleic acid sequence encoding PEDF or a therapeutic fragment thereof, wherein the adenoviral vector lacks all of the E1 region, part of the E3 region, and all of the E4 region in Paper No. 17, filed 6/20/03 is acknowledged. The traversal is on the ground(s) that for restriction to be proper that the inventions

must be independent or distinct as claimed and that there must be a serious burden on the Examiner if restriction is not required, and that the Office fails to meet the criteria and to present the required supporting evidence, failing to show separate classification, separate status in the art, or different field of search, and that the nature of the species set forth in the Restriction Requirement is such that a search for prior art related to one species likely would identify prior art of relevance to another species. It is argued that the Office has not even so much as alleged that there would be a serious burden on the Examiner if restriction is required and thus the Office has failed to meet the criterion for proper requirement for election of species.

This is not found persuasive because of the following reasons. The applicant is essentially arguing that the standards for restriction between independent or distinct inventions has not been applied to the requirement for election of species. The reason that the Office has not even so much as alleged that there would be a serious burden on the Examiner if restriction is required is because what is being required is election of species, one adenoviral vector species from among the ones claimed. The Examiner has fully set forth the USPTO-required form paragraphs concerning the elections of species,

which sets forth everything legally required as part of the election of species requirement. No argument concerning burden or independence or distinctness is needed, except for an indication that the claims are drawn to patentably distinct species. If the applicant disagrees that the species are patentably distinct, then the applicant can traverse on this basis. The only proper traversal of an election of species requirement that is fully set forth is an argument that the species are not patentably distinct, which the applicant has not done. See page 4, top paragraph of the Office communication mailed 5/20/03. Also, it is noted that as indicated at page 3, bottom paragraph of the Office communication mailed 5/20/03, upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species. The practical reason why elections of species are required is actually drawn to search and examination burden because a search for art concerning one specific species does not constitute a full search for art concerning other species because each species has to be searched for separately in non-patent literature searches, and thus when different claims are drawn to different species, additional searching is required to potentially reject all species of an invention that is taught by the prior art. The burden mostly goes away when it is determined that the generic

invention is allowable and thus a reasonable number of additional species are considered. In the instant case, a search for an adenovirus that lacks all of E1 and E4 and part of E3 does not necessarily identify that combination lacking all of the possible combinations concerning E2: all of E2, lacking part of E2, or lacking none of E2. There are a number of different permutations that would be burdensome to search if claimed separately as in the current claims.

The requirement is still deemed proper and is therefore made FINAL.

It is also noted that the earlier restriction election and elections of species, in Paper No. 6, filed 1/16/02 still apply and thus the elected and examined invention and species correspond to claims 1, 4-6, 8, 11-15, 18-21, 24-27, and 38-44.

Claims 9, 16-17, and 22-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6, filed 1/16/02 and Paper No. 17, filed 6/20/03.

Claim Rejections - 35 USC § 103

Claims 1, 4-6, 8, 11, 15, 21, 24-27, 38-41 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouck et al (U.S. Patent No. 6,288,024) in view of Cuthbertson (applicant reference AB) and Hardy (U.S. Patent No. 6,228,646 B1). This is a new rejection necessitated by the amendments to the claims filed 2/21/03 and 6/20/03.

Bouck et al teach a method of inhibiting angiogenesis within a tissue by providing exogenous SLED to cells associated with the tissue. SLED is defined as including any antiangiogenic derivative of PEDF (column 3), which encompasses both PEDF and therapeutic fragments thereof. This reference teaches that in one application, the tissue can be eye tissue, in which case the presence of exogenous SLED will inhibit novel angiogenesis associated with a variety of disorders of the eye (column 4). It is taught that within the context of the inventive method, SLED can be supplied alone or in conjunction with other known angiogenic factors, including dominant negative receptors for known inducers of angiogenesis, and that employing SLED in combination with other antiangiogenic agents can potentiate a more potent (and potentially synergistic) inhibition of angiogenesis within the desired tissue (column 5). This reference teaches that SLED polypeptide can be provided to

the tissue of interest by transferring an expression cassette including a nucleic acid encoding SLED to cells associated with the tissue of interest (column 6). The promoter that drives the expression of SLED is taught as being any appropriate promoter for use, including a CMV promoter, and that any suitable vector can be employed, such as adenoviral vectors (column 6).

Bouck et al do not specifically teach a specific, actually constructed embodiment of a replication-deficient adenoviral vector comprising a nucleic acid encoding PEDF or therapeutic fragment thereof, which vector lacking all of E1 and E4 and part of E3, and which vector can be used for a specific purpose, such as treatment of eye disease.

Cuthbertson teaches a method for generating a genetically-engineered in situ ocular cell, comprising contacting an ocular cell with an adenovirus vector which expresses a protein useful in the treatment of ocular disease (throughout the reference; column 2; claim 3). This reference teaches that the method can be used to treat a wide variety of conditions and diseases (column 5).

Hardy teaches a replication-deficient adenovirus vector containing deletions of all of E1, E2, E3, and E4 and use of CMV promoter to drive expression of a foreign gene (abstract; columns 4-5). This vector reads on an adenovirus vector lacking

part of E3 because part of E3 is deleted, along with another part, such that all of E3 is deleted. This reference teaches: that recombinant human adenoviruses have attracted much attention of late because of their potential for gene therapy and gene transfer and for protein expression in mammalian cells. First-generation recombinant adenovirus vectors most often contain deletions in the E1a and/or E1b regions. The usefulness of such vectors for gene transfer has been demonstrated in mice, cotton rats and nonhuman primates. A fundamental problem encountered in using these vectors for gene therapy, however, is that deletion of E1 sequences alone is not sufficient to completely ablate expression of other early and late viral genes or to prevent replication of the viral DNA. Studies have indicated that these vectors express viral antigens which elicit destructive immune responses in target cells (column 2). Newer recombinant adenovirus vectors contain additional disabling mutations in other regions of the adenovirus genome, for example in E2a or E3. These vectors, although they express fewer viral proteins, do not completely eliminate adenoviral protein expression and so are subject to similar immune response problems as found with earlier vectors. ... Another serious problem inherent in the use of current recombinant adenovirus-based vectors is their ability to recombine with adenoviruses

from natural sources to produce infections of wild type viruses. It would be advantageous to develop a recombinant adenovirus vector that is incapable of producing any adenovirus proteins, that can accommodate large inserts of foreign DNA and that recombines only at low frequency or not at all with other adenoviruses. The present inventor has surprisingly found that recombinant adenovirus (rAd) vectors containing as little as 600 base pairs of adenovirus sequence can be replicated and packaged in vivo to produce infectious viruses (column 3). It is an object of the present invention to provide therapeutic recombinant adenovirus-based (therapeutic rAd) vectors for gene therapy or for expression of foreign genes in mammalian cells. The therapeutic rAd vectors of the present invention contain a minimal amount of adenovirus DNA and are incapable of expressing any adenovirus antigens, i.e. "gutless". The therapeutic rAd vectors of the present invention provide the significant advantage of accommodating large inserts of foreign DNA while completely eliminating the problem of expressing adenoviral genes that result in an immunological response to viral proteins when a therapeutic rAd vector is used in gene therapy (columns 4-5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an adenovirus

vector comprising a nucleic acid encoding PEDF or therapeutic fragment thereof operatively linked to regulatory sequence necessary for expression (or further comprising a nucleic acid encoding other therapeutic substances such as other antiangiogenic substances), because Bouck et al teach that such vectors, including specifically mentioning adenovirus vectors, can be used to provide SLED to cells associated with the tissue of interest, that SLED will inhibit novel angiogenesis associated with a variety of eye disorders, including some disorders which are specifically mentioned by Cuthbertson, and Cuthbertson teaches that eye diseases can be treated with adenoviral vectors expressing a protein useful in the treatment of ocular disease. It would have been further obvious to modify the adenovirus vector made obvious from the teachings of Bouck et al and Cuthbertson by using as the base vector expressing SLED a gutless adenovirus vector as taught by Hardy because Hardy teaches use of gutless vectors for expressing foreign genes specifically for gene therapy.

One of ordinary skill in the art would have been motivated to do so for the expected benefit of specifically making an adenoviral vector which Cuthbertson teaches is a vector specifically useful to treat eye disease, to express SLED which Bouck et al teaches (using any of a number of vectors, including

adenovirus vector) is specifically useful for treating a variety of eye diseases. One would have been further motivated to use a gutless vector as the base adenoviral vector for expressing SLED because Hardy teaches the advantages of the gutless adenovirus vector for expressing foreign genes in gene therapy: the significant advantage of accommodating large inserts of foreign DNA while completely eliminating the problem of expressing adenoviral genes that result in an immunological response to viral proteins when a therapeutic rAd vector is used in gene therapy. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Regarding the use of a CMV promoter in the adenovirus vector to drive expression of SLED, it would have been obvious to do so because Bouck et al teaches that any suitable promoter can be used, including the CMV promoter, which is also taught by Hardy as a promoter that can drive expression of a foreign gene in the adenovirus vector.

Regarding the use of a gene encoding soluble VEGF receptor in the adenoviral vector, it would have been obvious to use any of the antiangiogenic genes that are and were well known in the art, including one encoding soluble VEGF receptor, because Bouck

et al teach to further include in the vector expressing SLED other known angiogenic factors, including dominant negative receptors for known inducers of angiogenesis, which encompasses soluble VEGF receptor.

Regarding the use of linking the therapeutic substance other than PEDF or therapeutic fragment thereof, to an ER localization signal peptide, it would have been obvious to do so because it is and was well known to do so in order to provide for the export of the substance, in order to enhance its therapeutic effect.

Claims 1, 4-6, 8, 11-12, 15, 21, 24-27, 38-41 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouck et al, Cuthbertson, and Hardy as applied to claims 1, 4-6, 8, 11, 15, 21, 24-27, 38-41 and 43-44 above, and further in view of Wickham et al (U.S. Patent No. 5,962,311). This is a new rejection necessitated by the amendments to the claims filed 2/21/03 and 6/20/03.

The teachings of Bouck et al, Cuthbertson, and Hardy are cited above and applied as before.

These three references do not specifically teach use of an LCR sequence as a cis-acting factor used to modulate the expression of PEDF in the adenovirus vector.

Palmiter et al teach the use of LCR elements in adenovirus vectors for gene therapy (column 11, and throughout the reference). This reference teaches that LCR sequences are ideal for obtaining regulated expression (column 11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the adenoviral vector made from the combined teachings of Bouck et al, Cuthbertson, and Hardy by using an LCR element to regulate the expression of SLED because Palmiter et al teach that it is within the ordinary skill in the art to use an LCR element to regulate expression in an adenovirus vector used for gene therapy and the other cited references teach an adenovirus vector for use in gene therapy.

One would have been motivated to do so for the expected benefit of making an adenovirus vector that has regulated expression of SLED by an LCR element which is taught by Palmiter et al as ideal for regulated expression in a gene therapy vector. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1, 4-6, 8, 11, 15, 18-21, 24-27, 38-41 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouck et al, Cuthbertson, and Hardy as applied to claims 1, 4-6, 8, 11, 15, 21, 24-27, 38-41 and 43-44 above, and further in view of Wickham et al (U.S. Patent No. 5,962,311). This is a new rejection necessitated by the amendments to the claims filed 2/21/03 and 6/20/03.

The teachings of Bouck et al, Cuthbertson, and Hardy are cited above and applied as before.

These three references do not specifically teach the adenoviral vector comprising a chimeric coat protein (which comprises a nonnative amino acid sequence) which directs entry into cells of the vector that is more efficient than wild type, which efficiently binds to a broader range of cells, and which binds an endogenous binding site not recognized by the wild type.

Wickham et al teach adenoviral vectors comprising a chimeric adenovirus fiber (which is a modified coat protein) (abstract; throughout the reference). This reference teaches that adenoviral vectors are preferred over other gene therapy vectors and that a drawback of the vectors in gene therapy is that all cells that comprise receptors for the adenoviral fiber and penton base will internalize the adenovirus and consequently

the genes being administered, not just the cells in need of therapeutic treatment (column 3). Wickham et al teach that limiting adenoviral entry to specific cells and/or expanding the repertoire of cells amenable to adenovirus-mediated gene therapy constitutes a substantial improvement over current technology (columns 3-4). This reference teaches how to accomplish this, through the modification of the adenoviral fiber by incorporation of non-native sequences for a ligand to a cell receptor (columns 4-5). Wickham et al teach that the method can be carried out to introduce adenovirus into any cell, even a cell that wild-type adenovirus binds and enters with relatively high efficiency (column 20).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the adenoviral vector made from the combined teachings of Bouck et al, Cuthbertson, and Hardy by making the vectors comprise a chimeric adenovirus fiber because Wickham et al teach that it is within the ordinary skill in the art to adenoviral vectors further comprising a chimeric coat protein having an inserted non-native sequence which directs the entry of the adenovirus to particular cells.

One would have been motivated to do so for the expected benefit of making an adenovirus vector that has limited

adenoviral vector entry and/or expanded range of cells that can be entered by the adenovirus, useful for more directly targeting the adenovirus to the cells in need of therapeutic treatment, overcoming a drawback of adenovirus for gene therapy, as taught by Wickham et al, for the adenoviral vectors made obvious from the combined teachings of the other cited references. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

The applicant argues that there is no teaching or reasonable suggestion in the cited references to combine their disclosures in the precise manner required to result in the present invention, that neither reference teaches the desirability of combining the teachings of the two references, let alone in the precise manner necessary to provide the present invention and that the Office has provided no actual evidence of a motivation to combine the prior art references. This argument is not persuasive because for every rejection under 35 USC 103(a) set forth in previous Office Actions and above, the motivation is clearly set forth in the paragraph starting: "One

(of ordinary skill in the art) would have been motivated to do so for the expected benefit of". This is the motivation that would have motivated one of ordinary skill in the art to combine the references, based upon what each reference teaches. Arguably, the teachings of the Cuthbertson reference are not needed to make obvious the claimed invention (except for the E regions deletion part of the rejection of the newly amended claims) because Bouck et al actually does teach an adenovirus encoding an expressible form of PEDF by teaching that any vector can be used to express SLED in cells, including specifically adenovirus (from a list of different vectors), and that expression of SLED can be used to treat eye disease. The reason that the Cuthbertson reference was added to the rejection was to show that use of adenovirus for expression of a gene encoding a protein used to treat eye disease (such as SLED taught by Bouck et al) is not just one vector from among many taught by Bouck et al, but instead that the prior art (Cuthbertson) considers that adenovirus is specifically a good vector for expression of a gene encoding a protein used to treat eye disease (and Cuthbertson provides enabling disclosure for use of an adenovirus vector expressing a foreign gene for treatment of eye disease). Thus, the Cuthbertson teaching of adenovirus expressing a therapeutic protein as a good gene therapy vector

for treating eye disease would have specifically motivated one of ordinary skill in the art to specifically select adenovirus vector from among the different vectors taught by Bouck as being useful for expressing SLED, such as for treating eye disease. The applicant did not address the clear motivation set forth in the rejections of record and thus the applicant's argument of lack of motivation set forth in the rejection is not persuasive. The obviousness and motivation to use a replication defective adenovirus vector to express PEDF is set forth in the new rejections above, as taught by Hardy.

The applicant's remaining arguments are drawn to the other cited references as not supplying the teachings or suggestions which are ascribed to Bouck et al and Cuthbertson in the rejections of record. The applicant's arguments are not persuasive in overcoming the rejections of record (now only the rejections as set forth above) because these other references were only relied upon for additional specific limitations found in some dependent claims, not for the core teachings of the claimed invention made obvious from the obvious combination of Bouck et al, Cuthbertson and (newly added Hardy). Therefore, in light of all available evidence, including the rejections set forth above, the applicant's arguments and the arguments set forth above, the claimed invention is still considered to have

been obvious and thus it is proper to maintain the rejections under 35 USC 103(a) set forth above.

Allowable Subject Matter

Claims 13-14 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 703-872-9306. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner

should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Terry A. McKelvey

Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

September 8, 2003